FUNCTIONAL LOCALIZATION OF AVIAN INTRAPULMONARY CO_2 RECEPTORS WITHIN THE PARABRONCHIAL MANTLE

by

WILLIAM DAVID CRANK

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Approved by:

Marion Roger Sedde

Major Professor

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDIX TABLES

INTRODUCTION

Bird lungs contain chemoreceptors sensitive to carbon dioxide (Peterson and Fedde, 1968). These receptors do not respond to mechanical stretch (Fedde et al., 1974) or hypoxia or hyperoxia (Fedde and Peterson, 1970), although they may respond slightly to H^+ (Powell et al., 1978). The adequate stimulus for these receptors is carbon dioxide (Burger et al., 1974). CO_2 receptors mediate a respiratory reflex which decreases breathing or causes apnea when intrapulmonary CO_2 concentration is reduced (Peterson and Fedde, 1971).

Histologically, afferent nerve endings within the lung have not been recognized as CO_2 receptors (King et al., 1974). Functional localization studies have shown that most CO_2 receptors are within the parabronchi, although these studies do not agree on the longitudinal distribution of the receptors (Osborne et al., 1977; Nye and Burger, 1978; Banzett and Burger, 1977; Scheid et al., 1974; Powell, 1978; Burger et al., 1974). No previous studies, to our knowledge, have functionally investigated the depth within the parabronchial mantle at which the CO_2 receptors might lie. Possible sites range from the luminal wall, through the intermingled air capillaries and blood capillaries, to the periphery of the parabronchus.

Our experiments were designed to functionally determine whether CO_2 receptors might be concentrated on the peripheral or luminal side of the parabronchial mantle.

THEORY

Functional Unit of Gas Exchange With Possible Receptor Locations

The chicken lung is composed of several hundred tubular parabronchi (King and Cowie, 1969). Ventilating gases flow through the parabronchial lumen, and gas exchange occurs in the mantle which surrounds the lumen. Blood capillaries and air capillaries are radially aligned within the mantle. Mixed venous blood becomes arterialized as it flows from the peripheral side of the mantle to the luminal side of the mantle (Duncker, 1974; Abdalla and King, 1975; West et al., 1977). O_2 and CO_2 move by diffusion within the air capillaries (Zeuthen, 1942) and they move by convection within the parabronchial lumen. The functional unit of gas exchange within a parabronchus has been modeled by a blood capillary adjacent to an air capillary which opens into the parabronchial lumen (fig. 1). This model is a subunit of the model of a complete parabronchus (Zeuthen, 1942; Scheid, 1978; Crank and Gallagher, 1978).

Possible CO_2 receptor sites within the functional unit are shown in fig. 1. A receptor in the wall of the parabronchial lumen would be influenced primarily by luminal gas. A receptor at the blood-gas interface would be influenced by blood as well as gas in its microenvironment. A receptor at the interface near the periphery of the mantle would be influenced by venous blood; a receptor at the interface near the parabronchial lumen would be influenced by arterialized blood. If CO_2 receptors are concentrated at either end of the capillaries, it should be possible to deduce their location by changing the PCO_2 profile along the blood capillaries and observing the resulting change in breathing pattern.

PCO_2 profiles along blood capillaries

Controlling the direction of perfusion, the PCO_2 of ventilating gas ($PgCO_2$), and the PCO_2 of perfusing blood ($PbCO_2$) allows a variety of PCO_2 profiles along a blood capillary to be obtained. During forward perfusion (flow from the peripheral to the luminal end of the blood capillary), when $PbCO_2$ is greater

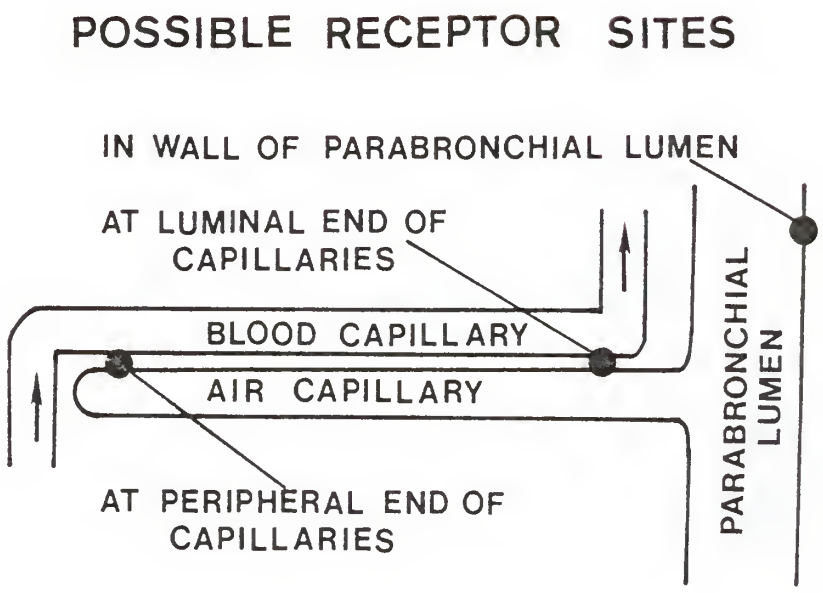

Fig. 1. The functional unit of gas exchange within a parabronchus showing possible CO_2 receptor locations.

than $PgCO_2$, the PCO_2 of blood decreases as it equilibrates with gas in the adjacent air capillary (fig. 2A, middle curve). Stopping ventilation while maintaining perfusion causes the entire lung to equilibrate with perfusing blood. The PCO_2 at the luminal end of a blood capillary rises to the same value as at the peripheral end (fig. 2A, upper curve). Stopping perfusion while maintaining ventilation causes the entire lung to equilibrate with ventilating gas. The PCO_2 of blood at the peripheral end of a blood capillary decreases to the same value as at the luminal end (fig. 2A, lower curve).

Figure 2B shows the PCO_2 profiles along a blood capillary which result during backward perfusion (flow from the luminal to the peripheral end of the blood capillary) when $PbCO_2$ is greater than $PgCO_2$. Figures 2C and 2D show the forward perfusion and backward perfusion profiles when $PgCO_2$ is greater than $PbCO_2$.

Localization of receptors by altering blood capillary PCO_2 profiles

Rationale of the experiment. Intrapulmonary CO_2 receptors affect breathing in a predictable way. Increasing intrapulmonary PCO_2 increases breathing amplitude (amplitude of sternal motion) and decreases breathing frequency (Ray and Fedde, 1969). A change in the PCO_2 profile along the blood capillaries may increase the PCO_2 within a restricted region of each blood capillary. If this change results in an increase in breathing amplitude and a decrease in breathing frequency, the implied CO_2 receptor location is the region of increased PCO_2. We have changed the blood capillary PCO_2 by three procedures: reversing the direction of blood capillary perfusion; stopping ventilation while maintaining perfusion; and stopping perfusion while maintaining ventilation.

Table 1 summarizes the receptor locations implied by the possible responses

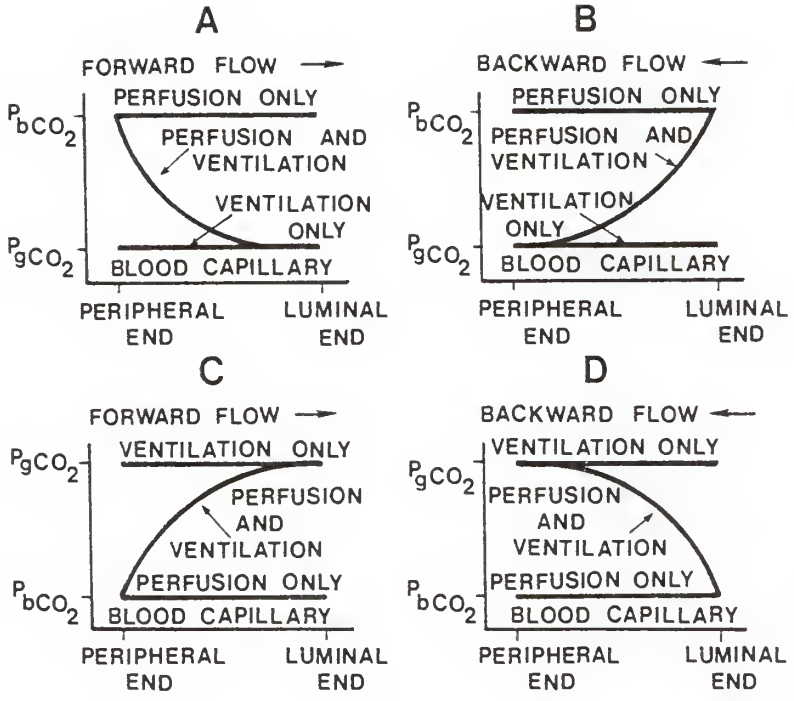

Fig. 2. PCO_2 profiles along blood capillaries under conditions of perfusion and ventilation, perfusion without ventilation, and ventilation without perfusion. A: forward perfusion when $PbCO_2$ is greater than $PgCO_2$, B: backward perfusion when $PbCO_2$ is greater than $PgCO_2$, C: forward perfusion when $PgCO_2$ is greater than $PbCO_2$, D: backward perfusion when $PgCO_2$ is greater than $PbCO_2$.

TABLE 1

RECEPTOR LOCATIONS IMPLIED BY POSSIBLE RESULTS

		Implied receptor location		
		1. Concentrated at peripheral end of capillaries	2. Concentrated at luminal end of capillaries	3. In wall of parabronchial lumen, or symmetrically distributed along capillaries
Reverse Perfusion	$PbCO_2 > PgCO_2$	$\Delta A < 0$, $\Delta F > 0$	$\Delta A > 0$, $\Delta F < 0$	$\Delta A = 0$, $\Delta F = 0$
	$PbCO_2 < PgCO_2$	$\Delta A > 0$, $\Delta F < 0$	$\Delta A < 0$, $\Delta F > 0$	$\Delta A = 0$, $\Delta F = 0$
Stop Ventilation	$PbCO_2 > PgCO_2$	$\Delta Af < \Delta Ar$, $\Delta Ff > \Delta Fr$	$\Delta Af > \Delta Ar$, $\Delta Ff < \Delta Fr$	$\Delta Af = \Delta Ar$, $\Delta Ff = \Delta Fr$
	$PbCO_2 < PgCO_2$	$\Delta Af > \Delta Ar$, $\Delta Ff < \Delta Fr$	$\Delta Af < \Delta Ar$, $\Delta Ff > \Delta Fr$	$\Delta Af = \Delta Ar$, $\Delta Ff = \Delta Fr$
Stop Perfusion	$PbCO_2 > PgCO_2$	$\Delta Af < \Delta Ar$, $\Delta Ff > \Delta Fr$	$\Delta Af > \Delta Ar$, $\Delta Ff < \Delta Fr$	$\Delta Af = \Delta Ar$, $\Delta Ff = \Delta Fr$
	$PbCO_2 < PgCO_2$	$\Delta Af > \Delta Ar$, $\Delta Ff < \Delta Fr$	$\Delta Af < \Delta Ar$, $\Delta Fr > \Delta Fr$	$\Delta Af = \Delta Ar$, $\Delta Ff = \Delta Fr$

$\Delta A > 0$ denotes an increase in breathing amplitude. $\Delta A < 0$ denotes a decrease in breathing amplitude. $\Delta F > 0$ denotes an increase in breathing frequency. $\Delta F < 0$ denotes a decrease in breathing frequency. Subscripts 'f' and 'r' signify forward perfusion and backward perfusion, respectively. The defining relations for ΔA and ΔF are given in Appendix A.

to the different procedures. Each row of the table consists of various possible responses to one particular treatment. Each column contains the one response from each of the various treatments which implies a particular receptor location. The first column of responses would imply that receptors are concentrated at the peripheral end of the blood capillaries; the second column of responses would imply that receptors are concentrated at the luminal end of the blood capillaries; and the third column of responses would imply that receptors are either distributed symmetrically along the blood capillary, or located in the wall of the parabronchial lumen. Symbols used in Table 1 are difined in Appendix A.

Reversal of perfusion. When $PbCO_2$ is greater than $PgCO_2$ (table 1, row 1) and the direction of perfusion is changed from forward to backward, figures 2A and 2B show that PCO_2 decreases at the peripheral end of the blood capillaries and increases at the luminal ends. If breathing amplitude decreases ($\Delta A < 0$) and breathing frequency increases ($\Delta F > 0$), the implied location of CO_2 receptors is the peripheral end of capillaries (table 1, column 1); if breathing amplitude increases ($\Delta A > 0$) and breathing frequency decreases ($\Delta F < 0$), the implied receptor location is the luminal end of capillaries (table 1, column 2). An unchanged breathing pattern ($\Delta A = 0$ and $\Delta F = 0$) is consistent with a symmetrical receptor distribution along the blood capillaries (table 1, column 3). When perfusion magnitude is unchanged, reversal of perfusion direction is predicted not to affect total gas exchange (Scheid, 1978); therefore, perfusion reversal should not change the PCO_2 of gas in the parabronchial lumen. Thus, an unchanged breathing pattern is also consistent with a receptor location in the walls of the parabronchial lumen (table 1, column 3).

Results of reversals from backward to forward are handled in the same way using equations 1 and 2 of Appendix A.

Possible results of perfusion reversal when $PbCO_2$ is less than $PgCO_2$ are given in table 1, row 2. The results are ordered into the appropriate columns according to implied receptor locations.

Stopping ventilation while maintaining perfusion. By unidirectionally ventilating birds, breathing efforts are decoupled from movement of gases through the lungs (see Methods). Thus, ventilation can be stopped while breathing motion continues.

When $PbCO_2$ is greater than $PgCO_2$ (table 1, row 3), stopping ventilation through the left lung while maintaining forward perfusion should cause the entire lung to increase to the PCO_2 of perfusing blood. Figure 2A shows the greatest increase along the blood capillaries to occur at their luminal ends. Stopping left lung ventilation while maintaining backward perfusion should cause PCO_2 to increase along the blood capillaries, the greatest increase occurring at their peripheral ends (fig. 2B). If the CO_2 receptors are located where they can sense the increased PCO_2, an increase in breathing amplitude ($\Delta Af > 0$) and a decrease in breathing frequency ($\Delta Ff < 0$) should result.

The change in breathing pattern which occurs when ventilation is stopped during forward perfusion is compared to the change in breathing pattern which occurs when ventilation is stopped during backward perfusion. An increase in breathing amplitude and a decrease in breathing frequency which is less exaggerated when ventilation is stopped during forward perfusion than during backward perfusion ($\Delta Af < \Delta Ar$ and $\Delta Ff > \Delta Fr$) imply a greater receptor density at the peripheral end of the blood capillaries (table 1, column1); an increase in breathing amplitude and a decrease in breathing frequency which is more exaggerated when ventilation is stopped during forward perfusion than during backward perfusion ($\Delta Af > \Delta Ar$ and $\Delta Ff < \Delta Fr$) imply a greater receptor density at the luminal end (table 1, column 2). Equal breathing changes when ventilation

is stopped during forward perfusion and backward perfusion ($\Delta Af = \Delta Ar$ and $\Delta Ff = \Delta Fr$) imply either a symmetrical distribution of receptors along the blood capillary or a location in the wall of the parabronchial lumen (table 1, column 3).

Possible responses to stopping ventilation when $PbCO_2$ is less than $PgCO_2$ are given in table 1, row 4. The results are ordered into the appropriate columns according to implied receptor location.

Stopping perfusion while maintaining ventilation. When $PbCO_2$ is greater than $PgCO_2$ (table 1, row 5), stopping forward perfusion while maintaining ventilation should cause the PCO_2 of static blood in the capillaries to decrease to the PCO_2 of ventilating gas. Figure 2A shows the greatest decrease to occur at the peripheral end of the blood capillaries. Stopping backward perfusion while maintaining ventilation should cause the PCO_2 to decrease along the blood capillaries, the greatest decrease occuring at the luminal ends of capillaries (fig. 2B). If the CO_2 receptors sense a decreased PCO_2, a decrease in breathing amplitude ($\Delta Af < 0$) and an increase in breathing frequency ($\Delta Ff < 0$) should result.

The change in breathing pattern which occurs when forward perfusion is stopped is compared to the change in breathing pattern which occurs when backward perfusion is stopped. A decrease in amplitude and increase in frequency which is more exaggerated when forward perfusion is stopped than when backward perfusion is stopped ($\Delta Af < \Delta Ar$ and $\Delta Ff > \Delta Fr$) implies a greater receptor density at the peripheral end of the blood capillaries (table 1, column 1); a decrease in amplitude and increase in frequency which is less exaggerated when forward perfusion is stopped than when backward perfusion is stopped ($\Delta Af > \Delta Ar$ and $\Delta Ff < \Delta Fr$) implies a greater receptor density at the luminal end of the blood capillaries (table 1, column 2). The occurrence of equal breathing changes when forward perfusion is stopped and when backward perfusion is stopped

($\Delta Af = \Delta Ar$ and $\Delta Ff = \Delta Fr$) implies a symmetrical distribution of receptors along the blood capillaries or a location in the lining of the parabronchial lumen (table 1, column 3).

Possible responses to stopping perfusion when $PbCO_2$ is less than $PgCO_2$ are given in table 1, row 6. The responses are ordered into the appropriate columns according to implied receptor location.

Thus, the ventilatory responses to the three methods of changing the CO_2 stimulus to various regions of the parabronchial mantle should provide a reliable estimate of the CO_2 receptor location within the gas exchange region of the lung.

METHODS

Animal preparation

Twenty-one White Leghorn male chickens (Babcock strain; 20 to 30 wks of age; avg. body wt. = 2.4 kg.) were anesthetized to a surgical plane with sodium pentobarbital which was initially given to effect (about 35 mg/kg) through the right cutaneous ulnar vein and thereafter given as needed in 5 mg doses. Body temperature was held at 41° C with a proportional temperature controller (YSI, thermistemp, model 71), by placing each bird supine on a heating pad and inserting a thermistor 10 cm into the rectum. Following tracheal cannulation, a ventral incision was made to expose the keel, the pectoral muscle was detached from the left side of the keel to expose the sternum; and the sternum was split to open the thoraco-abdominal cavity. All air sacs were immediately opened and unidirectional ventilation (see below) was begun. The left brachiocephalic artery was cannulated for the withdrawal of blood samples.

The left bronchus was cannulated about 1 cm below the syrinx for unidirectional ventilation of the left lung; the bronchus was then clamped just distal to the syrinx so that only the right lung was ventilated via the trachea. The left pulmonary artery was cannulated and about 5 ml of donor bird blood containing a smooth muscle relaxant (isoproterenol, 0.004 mg/ml of blood) was flushed into the lung. Then the left pulmonary vein was cannulated. Thus, the left lung, remaining in situ, was removed from the bird's circulatory system and incorporated into an extracorporeal circuit (see below) which had already been primed with blood. The right lung maintained the bird and held arterial blood gases constant while ventilation and perfusion of the left lung were experimentally manipulated. The opened thorax was covered with clear plastic to reduce heat loss and prevent drying. The innervation to both lungs remained intact.

Measurements

Arterial pressure was continuously measured with a pressure transducer (Statham model P23Gb) at the left brachiocephalic artery. Left bronchial gas pressure was measured on some birds with a pressure transducer (Statham, model P23BB) attached to a T-connection on the bronchial cannula. Sternal movement was measured with a force displacement transducer (Grass, FT10c) linked by a spring to the caudal tip of the sternum. These data were recorded on a multichannel pen recorder (Brush, model 481). Thermistors (YSI, model 511) were immersed in the blood flowing through the left pulmonary artery and vein, and temperatures were read from a meter (YSI, Tele-Thermometer, model 44TD).

Blood samples from the left brachiocephalic artery, left pulmonary vein, and left pulmonary artery were drawn into heparinized syringes that were capped and stored in ice water (less than 5 min.) until they could be analyzed.

Blood analysis was performed with a pH/gas analyzer (Instrumentation Laboratory, model 113) with the electrodes at 41° C. Pulmonary artery and vein PCO_2's were temperature corrected (Severinghaus, 1965).

The CO_2 concentration of gases ventilating the bird or the gas exchanger were measured with an infrared CO_2 analyzer (Beckman, LB-2). Gas samples were dried with $CaCO_3$ prior to measurement.

Extracorporeal circuit for lung perfusion

Figure 3 illustrates the extracorporeal circuit used to perfuse the left lung. Blood flowed under the force of gravity into the left lung from a reservoir, which was encased in a water jacket held at 41° C. With clamp 2 open and clamp 1 closed; blood flowed into the pulmonary artery and out the pulmonary vein (forward perfusion); with clamp 2 closed and clamp 1 open, blood flowed into the pulmonary vein and out the pulmonary artery (backward perfusion). From the lung, blood flowed to a bubbler gas exchanger, which was also encased in a water jacket held at 41° C (on the first 5 birds a Sci-med·Kolobcw, model 0200-2A membrane lung was used). The reservoir was positioned 25 to 35 cm above the left lung, which was approximately 35 cm above the gas exchanger. A peristaltic pump (Sigmamotor, T6S) lifted the blood from the gas exchanger to the reservoir. Pump speed was adjusted manually to minimize changes in the blood volume of the reservoir. Flow was determined by stopping the pump and timing a 10 ml decrease in reservoir volume.

The circuit was primed with about 250 ml blood from two or three donor birds before the lung was attached to it. The blood from donor birds, which were generally bled only once, contained heparin (about 130 units/ml blood).

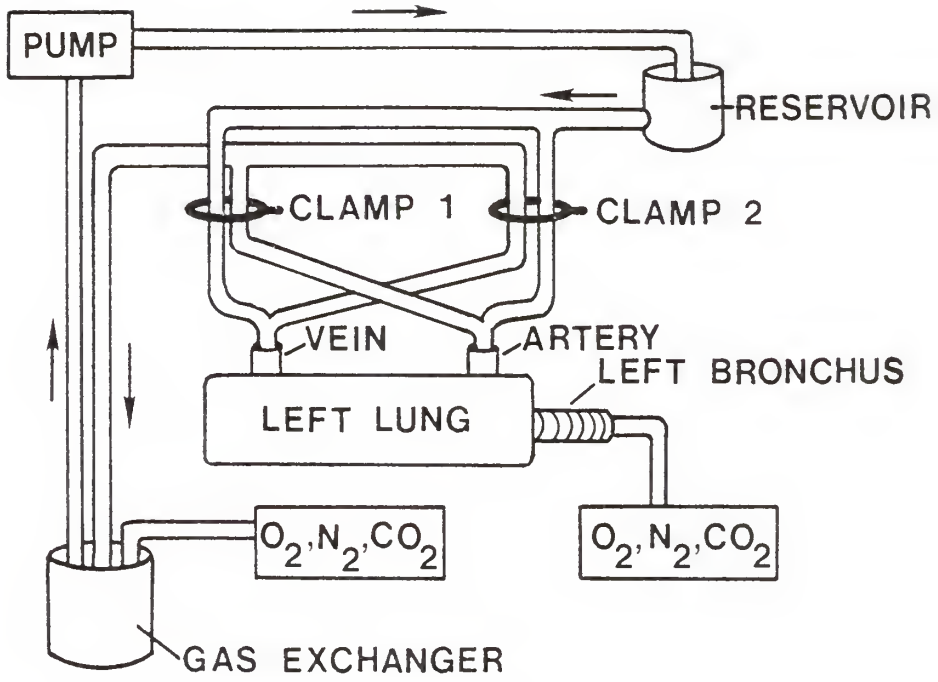

Fig. 3. Left lung ventilation and perfusion. Attachment of the left lung to the extracorporeal circuit containing a reservoir, gas exchanger, and pump is shown. Clamps 1 and 2 control the direction of perfusion of the lung. Ventilation of the left lung and the gas exchanger by gas mixtures is shown.

Ventilating gases

Gases were bubbled through water held at 39° C to condition them for the gas exchanger and the bird's lungs. Heated, humidified gases were transported through heated tubing to prevent heat loss and water condensation.

The composition of the gas mixture ventilating the gas exchanger was set by a mixing pump (Wosthoff model M-301/aF). A mixture of 70% N_2, 30% O_2, 0% CO_2 established low PCO_2 in the perfusing blood. A mixture of 60% N_2, 30% O_2, 10% CO_2 established high PCO_2 in the perfusing blood. Total flow was approximately 300 ml/min.

The O_2, N_2, and CO_2 components of the gas mixtures ventilating the bird's lungs were set with micrometer valves in line with rotometers. Each lung received 0.5 $L \cdot min^{-1}$ of O_2 and 1.5 $L \cdot min^{-1}$ of N_2. In the gas mixture ventilating the left lung, low PCO_2 was about 14 torr and high PCO_2 was about 56 torr. The PCO_2 of gas ventilating the right lung was adjusted so the bird was breathing with sufficiently great intensity that he could decrease breathing in response to a procedure, and with sufficiently small intensity that he could increase breathing in response to a procedure. Although the PCO_2 of right lung gas varied among the birds, it was generally not changed during the course of an experiment.

Criteria for data acceptance

Gas exchange in the left lung. For gas exchange to be present in the left lung, there must be flow through the lung and there must be a PCO_2 difference between inflowing blood and outflowing blood. When the blood flow through the lung became less than 50 ml/min, or when the PCO_2 difference between inflowing

blood and outflowing blood became less than 10 torr, the data were rejected and the experiment was stopped.

Functioning CO_2 receptors in the left lung. The integrity of the reflex arc from the CO_2 receptors, through the CNS, to the respiratory muscles was periodically tested by suddenly reducing the PCO_2 in the gas ventilating the left lung. Normally, a dramatic change in breathing amplitude and frequency resulted. No change indicated disruption of the reflex arc, and required that data be rejected and the experiment stopped.

Protocol

The protocol was begun if the bird satisfied the criteria for acceptance of data. The initial forward perfusion was reversed to backward perfusion. After a brief period of stable breathing with backward perfusion (abut 2 min.) ventilation was stopped while perfusion was maintained. This was continued until a new steady state breathing level was attained and sustained briefly (about 30 sec), then ventilation was resumed. After a stable breathing pattern was established again, backward perfusion was stopped while ventilation was maintained. This was also continued until a new steady state was attained and sustained briefly, then perfusion was resumed. After steady state was attained, perfusion was reversed from backward to forward; ventilation was stopped during forward perfusion, and forward perfusion was stopped during ventilation. Before and after each reversal the blood flow through the left lung was measured and samples of inflowing and outflowing blood were taken for blood gas analysis.

The entire process was repeated several times for most birds (the stop-ventilation or stop-perfusion procedures were not performed on some birds).

Before each repetition, the CO_2 receptor reflex was tested, temperatures of the blood flowing into the lung and out of the lung were measured, and arterial blood samples were taken. The experiment ended when one of the criteria for acceptance of data gave a negative result.

Data analysis

Data collection. The average respiratory frequency and amplitude of sternal deflection over 15 breaths immediately before reversal and 15 breaths following an 8 second delay after reversal were determined. During the delay, new steady state PCO_2 levels within the lung were established for the new flow direction. The average amplitude and frequency were substituted into equations 1 and 2 of Appendix A to obtain ΔA and ΔF.

The average frequency and amplitude were determined for 10 breaths immediately before stopping ventilation and 10 breaths immediately before resuming ventilation. Equations 3 and 4 of Appendix A yielded ΔA and ΔF.

The average frequency and amplitude were determined for 10 breaths immediately before stopping perfusion, the 10 breaths immediately before resuming perfusion, and 10 breaths following an 8 second delay after perfusion was resumed. Equations 5 and 6 of Appendix A yielded ΔA and ΔF when perfusion was stopped and when perfusion was resumed.

Statistics. When a procedure on a bird yielded several acceptable results, the ΔA's from that bird formed a statistical sample, and likewise with the ΔF's. The means of the samples from individual birds composed a sample of means. If only a single result was obtained from a bird, it became an element in the sample of means. Physiological conclusions have been drawn from the results of t-tests on the samples at the 5% significance level.

RESULTS

Perfusion reversal

The analysis of systemic arterial blood samples from those birds for which $PbCO_2$ was greater than $PgCO_2$ yielded the following means and standard deviations: pH = 7.41 $\pm$ .06, PO_2 = 118 $\pm$ 8 torr, PCO_2 = 41.9 $\pm$ 9.7 torr. From those birds for which $PgCO_2$ was greater than $PbCO_2$, the results were: pH = 7.43 $\pm$ .04, PO_2 = 110 $\pm$ 10 torr, PCO_2 = 38.0 $\pm$ 5.5 torr. The average temperature of perfusion blood, both flowing into the lung and flowing out, was 40° C.

The rate of blood flow was not significantly different before and after perfusion reversals (table 2), and the PCO_2 of blood leaving the lung was not significantly different before and after perfusion reversals (table 3).

A recording of sternal movement during the reversal of left lung perfusion is illustrated in figure 4. This tracing was typical of that exhibited by most birds in that breathing amplitude and frequency did not significantly change when perfusion was reversed. A statistically significant change in breathing amplitude of 3.5 percent occurred in one bird when perfusion was reversed. Statistically significant changes in breathing frequency of 3.5 and 1.9 percent occurred in two other birds. The mean and standard deviation of the set of mean responses from the various birds are given in table 4. Such results imply a symmetrical distribution of receptors along the capillaries, or a location in the lining of the parabronchial lumen.

Stopping ventilation while maintaining perfusion

Sternal movement recordings and simultaneous left bronchial gas pressure recording which were taken when left lung ventilation was suddenly stopped are

TABLE 2

RATE OF BLOOD FLOW THROUGH THE LEFT LUNG

	Forward Flow (ml/min) Mean ± S.D.	Backward Flow (ml/min) Mean ± S.D.	Magnitude Change at Reversal (Backward-Forward) Mean ± S.D.
$PbCO_2 < PgCO_2$	70.0 ± 12.8	69.5 ± 12.2	-0.5 ± 3.4
$PgCO_2 < PbCO_2$	74.4 ± 14.7	73.8 ± 14.5	-0.6 ± 3.7

TABLE 3

GAS EXCHANGE BY THE LEFT LUNG DURING FORWARD AND BACKWARD BLOOD FLOW

	Inflowing Blood PCO_2 (Torr) Mean ± S.D.	ΔPCO_2 During Forward Flow (Torr) Mean ± S.D.	ΔPCO_2 During Backward Flow (Torr) Mean ± S.D.	Backward Flow ΔPCO_2 - Forward Flow ΔPCO_2 Mean ± S.D.
$PbCO_2 > PgCO_2$	39.8 ± 5.8	-18.6 ± 4.2	-18.5 ± 4.9	0.1 ± 4.7
$PgCO_2 > PbCO_2$	24.6 ± 3.5	18.3 ± 3.1	17.1 ± 3.5	-1.2 ± 3.3

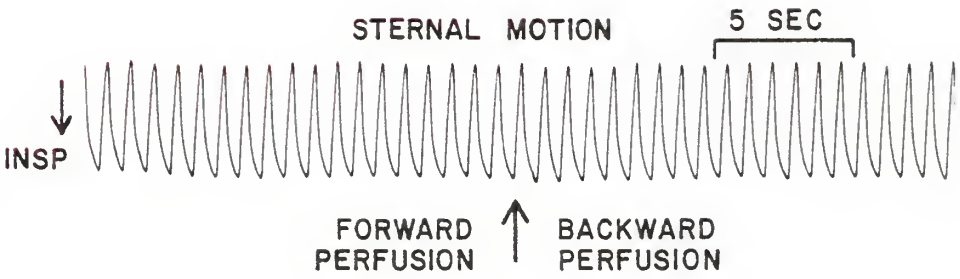

Fig. 4. The effect on sternal motion of reversing the direction of left lung perfusion when $PbCO_2$ is greater than $PgCO_2$.

TABLE 4

STERNAL MOTION RESPONSE TO PERFUSION REVERSAL

	No. of Birds	ΔA, % Mean of Means ± S.D. of Means	ΔF, % Mean of Means ± S.D. of Means
$PbCO_2$ > $PgCO_2$	9	-0.6 ± 1.5	0.2 ± 1.9
$PgCO_2$ > $PbCO_2$	12	0.1 ± 1.5	0.7 ± 1.5

illustrated in figure 5. Ventilation was stopped during the intervals of reduced bronchial gas pressure. When ventilation was stopped with $PbCO_2$ greater than $PgCO_2$, (figs. 5A and 5B), the lung equilibrated to the higher PCO_2 of perfusing blood, and breathing amplitude increased as breathing frequency decreased. When ventilation was stopped with $PgCO_2$ greater than $PbCO_2$ (fig. 5C and 5D), the lung equilibrated to the lower PCO_2 of perfusing blood, and breathing amplitude decreased as breathing frequency increased. The amplitude and frequency changes which occurred when ventilation was stopped during forward perfusion were not significantly different from the amplitude and frequency changes which occurred when ventilation was stopped during backward perfusion. This was true of all birds. The mean and standard deviation of the set of mean responses from the various birds are given in table 5. Such results imply a symmetrical distribution of receptors along the capillaries, or a location in the lining of the parabronchial lumen.

Stopping perfusion while maintaining ventilation

Sternal movement recordings which were taken when left lung perfusion was suddenly stopped are illustrated in figure 6. When perfusion was stopped with $PbCO_2$ greater than $PgCO_2$ (fig. 6A and 6B), the lung equilibrated to the lower PCO_2 of ventilation gas. Breathing amplitude decreased as breathing frequency increased. When perfusion was stopped with $PgCO_2$ greater than $PbCO_2$ (fig. 6C and 6D), the lung equilibrated to the higher PCO_2 of ventilating gas and breathing amplitude was expected to increase as breathing frequency decreased. In fact, the changes in breathing pattern were slight or non-existent. The amplitude and frequency changes which occurred after stopping forward perfusion were not significantly different from the amplitude and frequency changes which occurred after stopping backward perfusion. This was true of all birds. The

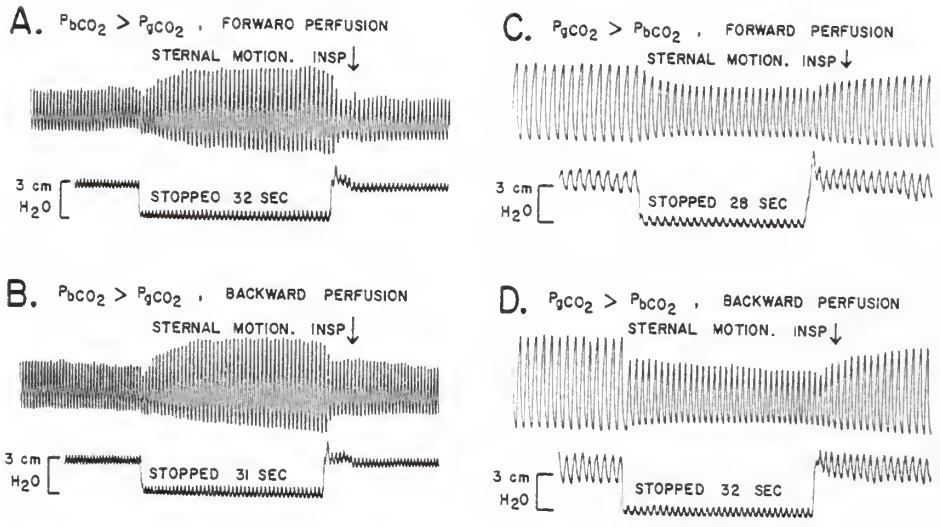

Fig. 5. The simultaneous effects on sternal motion and left bronchial gas pressure when left lung ventilation was stopped. A: forward perfusion when $PbCO_2$ was greater than $PgCO_2$, B: backward perfusion when PbCO2 was greater than $PgCO_2$, C: forward perfusion when $PgCO_2$ was greater than $PbCO_2$, D: backward perfusion when $PgCO_2$ was greater than $PbCO_2$.

TABLE 5

STERNAL MOTION RESPONSE TO STOPPING VENTILATION WHILE MAINTAINING PERFUSION

	Forward Perfusion			Backward Perfusion		
	No. of Birds	ΔA, % Mean of Means ± S.D. of Means	ΔF, % Mean of Means ± S.D. of Means	No. of Birds	ΔA, % Mean of Means ± S.D. of Means	ΔF, % Mean of Means ± S.D. of Means
$PbCO_2$ > $PgCO_2$	8	46.6 ± 31.9	-13.7 ± 7.3	8	44.9 ± 26.2	-12.7 ± 7.7
$PgCO_2$ > $PbCO_2$	8	-25.9 ± 9.9	17.3 ± 13.9	6	-24.9 ± 12.5	13.5 ± 13.8

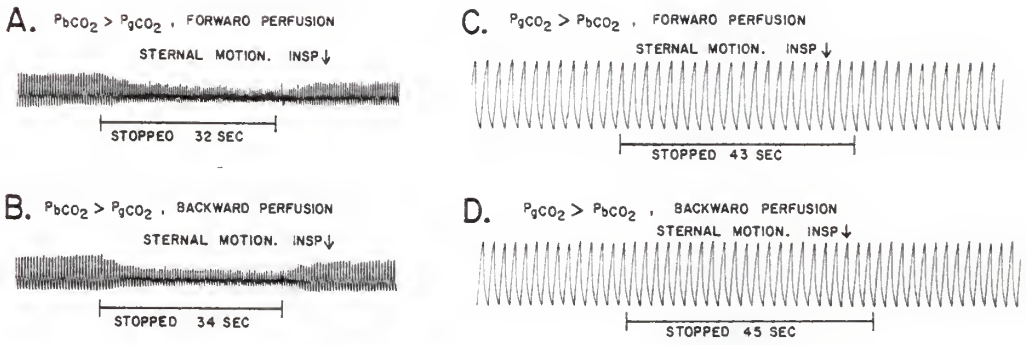

Fig. 6. The effect on sternal motion when left lung perfusion was stopped. A: forward perfusion when $PbCO_2$ was greater than $PgCO_2$, B: backward perfusion when $PbCO_2$ was greater than $PgCO_2$, C: forward perfusion when $PgCO_2$ was greater than $PbCO_2$, D: backward perfusion when $PgCO_2$ was greater than $PbCO_2$.

TABLE 6

STERNAL MOTION RESPONSE TO STOPPING PERFUSION WHILE MAINTAINING VENTILATION

	Forward Perfusion			Backward Perfusion		
	No. of Birds	ΔA, % Mean of Means ± S.D of Means	ΔF, % Mean of Means ± S.D. of Means	No. of Birds	ΔA, % Mean of Means ± S.D. of Means	ΔF, % Mean of Means ± S.D. of Means
$PbCO_2 > PgCO_2$	8	-15.3 ± 11.4	7.1 ± 6.3	8	-14.6 ± 13.4	6.8 ± 8.5
$PgCO_2 > PbCO_2$	7	1.0 ± 1.9	2.0 ± 3.8	4	1.2 ± 2.0	0.3 ± 1.3

mean and standard deviation of the set of mean responses from the various birds are given in table 6. Such results imply a symmetrical distribution of receptors along the capillaries, or a location in the lining of the parabronchial lumen.

Deterioration of the preparation

Each experiment was halted when the bird failed a test for acceptance of data. A few birds deteriorated by failing the test for integrity of the CO_2 receptor reflex arc. Most birds deteriorated when blood flow through the left lung slowed. One bird deteriorated when the left lung ceased to perform gas exchange, although blood flow through the lung remained high and the reflex arc continued to function.

Vagotomy

Data were obtained from a few birds before and after section of the right vagus. There was no significant difference between pre- and post-vagotomy results for any of the procedures in the protocol.

Summary of results from individual birds

Those birds from which sufficient results were obtained to do statistical comparisons are ordered in table 7 according to the CO_2 receptor locations which they imply. Results of t-tests on amplitude and frequency results are shown separately. These results nearly unanimously imply that the receptors are either distributed symmetrically along the blood capillaries or located in the parabronchial lumen.

TABLE 7

NUMBER OF BIRDS WHOSE RESPONSES (ΔA or ΔF) IMPLY VARIOUS CO_2 RECEPTOR LOCATIONS.

Procedures		Peripheral end of capillaries		Luminal end of capillaries		Symmetrical distribution or parabronchial luminal wall	
		ΔA No. of Birds	ΔF No. of Birds	ΔA No. of Birds	ΔF No. of Birds	ΔA No. of Birds	ΔF No. of Birds
Perfusion	$PbCO_2$ > PgCO2	1	1	0	0	8	8
Reversal	$PgCO_2$ > PbCO2	0	1	0	0	12	11
Stop	$PbCO_2$ > $PgCO_2$	0	0	0	0	7	7
Ventilation	$PgCO_2$ > $PbCO_2$	0	0	0	0	6	6
Stop	$PbCO_2$ > $PgCO_2$	0	0	0	0	7	7
Perfusion	$PgCO_2$ > $PbCO_2$	0	0	0	0	4	4

DISCUSSION

Critique of methods and assumptions

Symmetrical reversal of blood capillary PCO_2 profiles. It is desirable that perfusion reversal cause a symmetrical reversal of the blood capillary PCO_2 profile so that the CO_2 stimulus applied to one end of the capillary before reversal be the same as the CO_2 stimulus applied to the other end of the capillary after reversal. Otherwise, a change in breathing pattern could be due to a nonsymmetrical CO_2 receptor distribution or a nonsymmetrical reversal of CO_2 stimulus. Similar considerations apply to stop-ventilation and stop-perfusion procedures.

Assuming a neglibible PCO_2 variation within air capillaries, symmetrical reversal of the PCO_2 profile along blood capillaries is implied to have occurred if gas exchange was the same during forward and backward perfusion. Gas exchange was the same if perfusion reversal changed neither the magnitude of blood flow through the lung nor the PCO_2 difference between inflowing and outflowing blood. Since the magnitude of blood flow (table 2) and the PCO_2 difference (table 3) were unchanged, we believe the PCO_2 profiles were symmetrically reversed.

PCO_2 variation along air capillaries. Air capillary PCO_2 has not yet been measured. However, model calculations (Crank and Gallagher, 1978) have estimated the PCO_2 along air capillaries to vary less than one torr from end to end at a resting perfusion rate. The left lung perfusion in our experiments was about 70 $ml \cdot min^{-1}$ (table 3), which is less than that of resting chickens (Vogel and Sturkie, 1963). At the same CO_2 exchange rate, PCO_2 along the air capillaries varies even less during backward perfusion because more CO_2 diffuses from blood into the luminal end of the air capillary than into the peripheral end. Hence,

the effect of PCO_2 variation within air capillaries on blood capillary PCO_2 profiles is negligible.

Blood and gas influences on CO_2 receptors in the mantle. Figure 5 of McLelland et al., 1972, shows an axon lying between an air capillary and a blood capillary. If the CO_2 receptor is an axonal ending similarly situated between an air capillary and a blood capillary, it should be directly influenced by the PCO_2 of blood and gas.

Uncertainty of parabronchial ventilation. The left lung was ventilated at 2 $L \cdot min^{-1}$, but the ventilating gas divided in an unknown manner among parabronchial gas exchange regions, escape by way of caudal air sac ostia, and escape by way of cranial air sac ostia. Although we do not know quantitatively the flow of gas through the parabronchi, the presence of left lung gas exchange implies that the parabronchi were ventilated. When left lung perfusion was 70 $ml \cdot min^{-1}$ (table 2), the PCO_2 of blood changed by 18 torr as a result of intrapulmonary gas exchange (table 3).

Steady state breathing levels. When ventilation was stopped, the breathing pattern changed rapidly at first, then the rate of change slowed (fig. 5). Sometimes when ventilation was resumed after 30 sec., the breathing pattern was still changing very slowly. This quasi-steady state breathing level was used in the data analysis, since its rate of change was very small after 30 sec. The same considerations apply for stopping perfusion.

Right vagotomy. In another study of CO_2 receptor location in the left lung (Powell, 1978), the right vagus was severed to eliminate variable influences on the CNS from the right lung. To achieve the same end in our experiments the composition of the gas ventilating the right lung remained constant during experimental procedures. As a check, data were obtained from several birds before

and after right vagotomy. The birds' responses to experimental procedures were not significantly altered by right vagotomy.

Chemoreceptors or mechanoreceptors

Stopping left lung ventilation when $PbCO_2$ was greater than $PgCO_2$ reduced intrapulmonary gas pressure and increased intrapulmonary PCO_2, which increased breathing amplitude (fig. 5A and 5B). Stopping left lung ventilation when $PgCO_2$ was greater than $PbCO_2$ reduced intrapulmonary gas pressure and decreased intrapulmonary PCO_2 (fig. 5C and 5D). Breathing followed the changes in PCO_2, not intrapulmonary pressure, implying that putative intrapulmonary stretch receptors (Leitner and Roumy, 1974) were not affecting the response.

Gas exchange during backward perfusion

Gas exchange is unaltered by the reversal of blood flow direction through the lung (tables 2 and 3). This would happen if the PCO_2 were constant within air capillaries and the constancy did not change upon perfusion reversal, since blood would then be exposed to the same homogeneous medium regardless of flow direction. In fact, model calculations (Crank and Gallagher, 1978) have estimated the PCO_2 variation within air capillaries to be small under resting conditions. Other theorectical considerations (Scheid, 1978) imply that even were the PCO_2 variation within air capillaries to be large, the same gas exchange would occur during forward and backward perfusion at equal flows. The results obtained do not test this latter prediction because the gas exchange rate was too low to elevate the PCO_2 gradient along air capillaries.

Control of pulmonary blood flow

Possible arteriolar sphincters surrounding the precapillary blood vessels have been observed histologically (Abdalla and King, 1975). Contraction or relaxation of this muscle might regulate pulmonary blood flow. A possible stimulus for muscle control is the PCO_2 of the microenvironment. However, the results show that the magnitude of blood flow through the lung does not change (table 2) when the PCO_2 at the precapillary region (peripheral end of capillaries) is changed (table 3) by reversal of direction of blood flow. Although these results imply no control of pulmonary blood flow by local PCO_2 levels, this conclusion is compromised by the presence of a muscle relaxant, isoproterenol, in the perfusion blood.

CO_2 receptors: symmetrical distribution along capillaries or location in parabronchial luminal epithelium?

Although the primary observations of the experiment impartially imply either a symmetrical distribution of receptors along the capillaries or a location in the epithelial lining of the parabronchial lumen, secondary observations favor the location in the luminal epithelium.

When perfusion is stopped while ventilation is continued, the PCO_2 change within the mantle can be as great as the difference between the PCO_2 of perfusion blood and the PCO_2 of ventilation gas, but the PCO_2 change within the parabronchial lumen depends upon the magnitude of ventilation compared to perfusion. The greater the ventilation the less the intraluminal PCO_2 change. The changes in breathing pattern which occur when perfusion is stopped while ventilation is continued could be due to sensation of PCO_2 changes by CO_2 receptors in the mantle or in the lumen. A small change in breathing pattern

might imply that the CO_2 receptors sense a small PCO_2 change because they are located in the parabronchial lumen and the parabronchial ventilation is high. A very small change in breathing pattern did result from stopping perfusion while continuing ventilation when $PgCO_2$ was greater than $PbCO_2$ (fig. 6C and 6D, and table 6). Since larger changes in breathing pattern were obtained when $PbCO_2$ was greater than $PgCO_2$ (fig. 6A and 6B, and table 6), the implication that CO_2 receptors are located in the luminal epithelium is not unequivocal.

One bird deteriorated when the left lung stopped performing gas exchange, although blood flow remained high. The cessation of gas exchange implies that blood was not being exposed to gas in the lung, perhaps because the air capillaries were filled with edematous fluid. If this were so, changes in CO_2 level of ventilating gases would impinge on the parabronchial luminal surface, but not penetrate into the mantle. Because the bird responded to changes in CO_2 level of the ventilating gas after deterioration of gas exchange, the implied CO_2 receptor location is the epithelial lining of the parabronchial lumen.

In summary, the principle results of the experiment imply that CO_2 receptors are either distributed symmetrically between the peripheral and luminal sides of the parabronchial mantle, or located in the epithelial lining of the parabronchial lumen. Secondary results tend to favor the location in the luminal epithelium.

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Appendix A. Calculation of ΔA and ΔF

When an experimental procedure is performed, there may be a change in breathing amplitude (ΔA) or a change in breathing frequency (ΔF). Upon reversing perfusion, either from forward to backward or from backward to forward, ΔA and ΔF are calculated as:

(1) $\Delta A = (A_{backward} - A_{forward})/A_{forward}$,

(2) $\Delta F = (F_{backward} - F_{forward})/F_{forward}$.

Upon stopping ventilation while maintaining perfusion, ΔA and ΔF are calculated as:

(3) $\Delta A = (A_{without\ ventilation} - A_{with\ ventilation})/A_{with\ ventilation}$,

(4) $\Delta F = (F_{without\ ventilation} - F_{with\ ventilation})/F_{with\ ventilation}$.

Upon stopping perfusion while maintaining ventilation, ΔA and ΔF are calculated as:

(5) $\Delta A = (A_{without\ perfusion} - A_{with\ perfusion})/A_{with\ perfusion}$,

(6) $\Delta F = (F_{without\ perfusion} - F_{with\ perfusuion})/F_{with\ perfusion}$.

Equations (5) and (6) are also used to calculate ΔA and ΔF when perfusion is resumed. Subscripts "f" and "r" are applied to ΔA and ΔF as defined in equations (3), (4), (5), and (6), when the perfusion direction is forward or backward, respectively.

APPENDIX TABLE 1

SUMMARY OF RESULTS FOR PERFUSION REVERSAL FROM ALL BIRDS

$PbCO_2$ greater than $PgCO_2$				$PgCO_2$ greater than $PbCO_2$			
No. of Birds	No. of Trials	ΔA Mean ± S.D. Percent	ΔF Mean ± S.D. Percent	No. of Birds	No. of Trials	ΔA Mean ± S.D. Percent	ΔF Mean ± S.D. Percent
2	4	-1.1 ± 3.0	-1.7 ± 2.2	1	2	-0.2 ± 2.4	2.8 ± 3.0
9	6	0.2 ± 2.1	0.2 ± 1.5	3	4	2.3 ± 2.5	-0.2 ± 0.9
11	1	-0.8	1.8	4	2	-0.0 ± 1.1	3.4 ± 5.9
12	5	-1.1 ± 2.3	-0.3 ± 1.8	5	2	-3.3 ± 8.4	0.4 ± 0.6
13	9	1.1 ± 4.8	0.2 ± 2.5	6	14	1.1 ± 2.5	0.6 ± 5.4
14	1	-0.1	0.2	7	12	0.6 ± 2.3	0.9 ± 4.1
16	6	1.6 ± 4.9	1.2 ± 2.3	8	7	0.4 ± 2.0	0.2 ± 0.5
18	4	-1.7 ± 5.5	3.5 ± 2.0*	10	4	-1.1 ± 5.2	1.6 ± 2.7
20	13	-3.5 ± 2.6*	-3.0 ± 4.9	15	8	0.5 ± 1.1	0.4 ± 1.5
				17	6	1.7 ± 3.1	-1.9 ± 1.8*
				19	5	-1.6 ± 1.5	-1.0 ± 2.5
				21	6	1.2 ± 5.4	1.5 ± 3.5
Mean of means ± S.D.		-0.6 ± 1.5	0.2 ± 1.9	Mean of Means ± S.D.		0.1 ± 1.5	0.7 ± 1.5

*Significantly different from zero.

APPENDIX TABLE 2

SUMMARY OF RESULTS FOR STOPPING VENTILATION WHILE MAINTAINING PERFUSION FROM ALL BIRDS

	Forward Perfusion			Backward Perfusion		
No. of Birds	No. of Trials	ΔAf Mean ± S.D. Percent	ΔFf Mean ± S.D. Percent	No. of Trials	ΔAb Mean ± S.D. Percent	ΔFb Mean ± S.D. Percent
	$PbCO_2$ Greater than $PgCO_2$					
9	10	39.5 ± 16.2	- 6.3 ± 8.4	1	62.5	-11.2
11	0	- - - - - -	- - - - - -	1	7.0	0.0
12	2	12.7 ± 8.6	- 5.4 ± 4.7	4	19.9 ± 8.1	- 6.2 ± 3.2
13	3	32.0 ± 6.4	-12.3 ± 1.4	3	45.0 ± 24.3	-14.9 ± 5.1
14	2	51.9 ± 13.8	-23.4 ± 4.5	3	54.4 ± 11.6	-18.7 ± 9.8
16	3	40.5 ± 6.1	- 9.1 ± 5.6	6	42.4 ± 28.2	-11.6 ± 3.4
18	7	113.8 ± 39.3	-21.8 ± 14.2	9	92.4 ± 42.8	-25.7 ± 7.9
20	7	35.8 ± 16.3	-17.7 ± 17.1	6	35.6 ± 27.9	-13.0 ± 18.3
Mean of means ± S.D.		46.6 ± 31.9	-13.7 ± 7.3		44.9 ± 26.2	-12.7 ± 7.7
	$PgCO_2$ Greater than $PbCO_2$					
6	10	-32.3 ± 15.8	22.8 ± 19.3	0	- - - - - -	- - - - - -
7	5	-19.3 ± 9.8	36.3 ± 6.2	0	- - - - - -	- - - - - -
8	3	-26.3 ± 16.9	- 0.6 ± 2.9	2	-16.8 ± 4.4	0.8 ± 1.2
10	3	-16.4 ± 6.9	9.0 ± 4.6	1	-16.5	10.8
15	3	-32.9 ± 14.7	10.9 ± 7.0	4	-30.2 ± 13.3	10.6 ± 4.6
17	9	-38.4 ± 11.7	35.8 ± 15.3	8	-46.2 ± 8.2	38.3 ± 4.9
19	4	- 9.2 ± 2.6	3.6 ± 0.7	6	-12.4 ± 10.7	2.1 ± 2.8
21	3	-32.2 ± 6.4	21.0 ± 15.0	3	-27.3 ± 12.5	18.6 ± 7.3
Mean of means ± S.D.		-25.9 ± 9.9	17.3 ± 13.9		-24.9 ± 12.5	13.5 ± 13.8

APPENDIX TABLE 3

SUMMARY OF RESULTS FOR STOPPING PERFUSION WHILE MAINTAINING VENTILATION FROM ALL BIRDS

	Forward Perfusion Stopped			Backward Perfusion Stopped		
No. of Birds	No. of Trials	ΔAf Mean ± S.D. Percent	ΔFf Mean ± S.D. Percent	No. of Trials	ΔAb Mean ± S.D. Percent	ΔFb Mean ± S.D. Percent
	$PbCO_2$ Greater than $PgCO_2$					
9	34	- 9.4 ± 9.3	6.8 ± 7.5	8	- 7.7 ± 6.6	5.6 ± 5.8
11	0	- - - - -	- - - - -	8	- 7.9 ± 2.7	0.6 ± 0.0
12	2	-10.7 ± 1.5	5.2 ± 0.9	6	-10.6 ± 3.9	6.1 ± 5.0
13	6	-14.3 ± 4.7	4.0 ± 2.7	8	-19.2 ± 10.5	9.4 ± 7.6
14	4	- 1.5 ± 2.8	5.3 ± 2.4	4	- 2.6 ± 5.1	4.1 ± 5.7
16	6	-12.8 ± 6.6	4.8 ± 2.1	6	- 8.8 ± 10.5	3.2 ± 7.3
18	14	-37.9 ± 11.9	21.0 ± 12.1	16	-45.4 ± 12.6	26.4 ± 11.3
20	10	-20.2 ± 9.1	2.7 ± 10.0	12	-14.9 ± 10.1	-9.8 ± 7.1
Mean of means ± S.D.		-15.3 ± 11.4	7.1 ± 6.3		-14.6 ± 13.4	6.8 ± 8.5
	$PgCO_2$ Greater than $PbCO_2$					
6	14	- 1.9 ± 6.7	6.3 ± 5.7	0	- - - - - -	- - - - - -
7	12	0.9 ± 3.0	8.3 ± 5.1	0	- - - - - -	- - - - - -
8	4	0.1 ± 7.6	-0.6 ± 3.9	0	- - - - - -	- - - - - -
10	14	4.5 ± 9.3	-0.3 ± 2.4	4	3.7 ± 4.7	1.0 ± 3.2
15	6	1.7 ± 4.8	1.5 ± 2.1	5	1.4 ± 3.0	1.7 ± 1.5
19	8	0.7 ± 2.3	-0.8 ± 2.8	10	0.9 ± 2.3	-1.0 ± 6.4
21	14	0.7 ± 3.7	-0.7 ± 3.6	12	-1.1 ± 5.7	-0.5 ± 4.6
Mean of means ± S.D.		1.0 ± 1.9	2.0 ± 3.8		1.2 ± 2.0	0.3 ± 1.3

FUNCTIONAL LOCALIZATION OF AVIAN INTRAPULMONARY CO_2 RECEPTORS WITHIN THE PARABRONCHIAL MANTLE

by

WILLIAM DAVID CRANK

B.S., Kansas State University, 1968

M.S., Kansas State University, 1978

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requirements for the degree

MASTER OF SCIENCE

Department of Anatomy and Physiology

KANSAS STATE UNIVERSITY
Manhattan, Kansas

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To determine the location of avian intrapulmonary CO_2 receptors, we changed the CO_2 stimulus at different regions within the parabronchial mantle and measured the resulting changes in breathing pattern. Three procedures were used to vary the CO_2 stimulus: 1) Reverse the direction of pulmonary perfusion; 2) stop pulmonary ventilation while maintaining perfusion; and 3) stop pulmonary perfusion while maintaining ventilation.

Right and left lungs of adult, anesthetized white Leghorn type chickens were independently, unidirectionally ventilated. The right lung was used to maintain the bird while the left pulmonary artery and vein were cannulated and connected to an extracorporeal gas exchanger, thereby isolating this lung's perfusion. The innervation to both lungs remained intact.

When left pulmonary perfusion was reversed the birds breathing pattern remained umchanged. The change in breathing pattern which resulted from stopping left pulmonary ventilation was the same during forward perfusion (pulmonary artery to pulmonary vein) as during backward perfusion (pulmonary vein to pulmonary artery). The change in breathing pattern which resulted from stopping forward perfusion was the same as that resulting from stopping backward perfusion. The results indicate that CO_2 receptors are not concentrated on the peripheral side of the parabronchial mantle where venous blood would influence them, or on the luminal side of the mantle where arterialized blood would influence them. The CO_2 receptors are either distributed symmetrically between the peripheral and luminal sides of the mantle or located in the epithelial lining of the parabronchial lumen.